Caprice Greystoke

"Thinking About Tomorrow...Today!"

October 10, 1994

Dr. David Kessler
Commissioner of the Food and Drug Administration
Room 14-71, 5600 Fishers Lane
Rockville, MD 20857

Re: 21 CFR 54, 312, 314, 320, 330, 601, 807, 812, 814 and 860
DOCKET NO. 93N-0445

PROPOSED RULE 21 CFR
FINANCIAL DISCLOSURE BY CLINICAL INVESTIGATORS
FOOD AND DRUG AGENCY HHS

Dear Commissioner Kessler;

Further to my letter to you of September 20, 1994; Caprice Greystoke respectfully submits the following comments and documents that are relevant to the above Proposed Rule, to show, existing past and present, conflicts of interest within the FDA. In addition to the comments to the above Proposed Rule, Caprice Greystoke respectfully asks that the following also be entered as the **Second Amendment to Citizen's Petition Dockets Numbered 82N-022/CP17 and 76N-052N/CP15**.

On August 1, 1994, Caprice Greystoke issued a **Citizen's Petition**, Dockets Numbered 81N-022 and 76N-052N addressing its concern of conflicts of interest prevalent in the FDA Office of Over-The-Counter Drug Evaluation. These conflicts of interest are obvious and would appear to be the only possible reason for an 180° turnaround, of a proposed rule within the Final Rule of August 8, 1991, by a letter from William Gilbertson to the NDMA dated May 20, 1994.

On August 23, 1994, the FDA issued a Final Rule deferring PPA back to 1976.

On September 20, 1994, Caprice Greystoke issued an **Amendment** to its August 1, 1994, **Citizen's Petition 82N-0022 and 76N-052N**, in response to the FDA Final Rule deferment, stating: "the obvious perception is that this branch of the FDA is more interested in the profits of the drug companies than the safety of the public" (see **Amendment to Caprice Greystoke's Citizen's Petition** Page 6, Number 10). (enclosures)

On September 22, 1994, the FDA issued the above **captioned Proposed Rule**.

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Caprice Greystoke thanks the FDA for their indirect backhand response, to its Citizen's Petition and Amendment, but as usual it skirts the main problem, which is within the Office of Over-The-Counter Drug Evaluation, that have allowed these conflicts of interest to exist over many years. It is incumbent upon the FDA to get its own house in order rather than continue to issue Proposed Rules and Final Rules that accomplish very little, except to protect its own backside for **past offenses**.
The idea of financial disclosure by clinical investigators is a good one, **but does not go far enough**.

1. The heading should include and emphasize - **any conflict of interest**.
2. Should include **all FDA officials**.
3. Should include **all lobbying groups that represent the drug manufacturers**.
4. Should include **all drug manufacturers**.
5. Should be made **retroactive** if shown that a conflict of interest was present at any time before any Proposed or Final Ruling - then it should be dealt with accordingly.
6. The dollar amount is not relevant as percents are not relevant - **a conflict of interest is a conflict of interest**. What may be a significant amount of dollars to one may not be significant to another.
7. Studies should not be worded with ambiguous phrases. Example: when referring to a controversial drug in a time release capsule "20 mg Phenylpropanolamine.HCl which dissolves as a standard immediate release formulation, the remaining 55 mg leave the OROS tablet slowly over approximately 16 hours". Dosages that are administered with a drug of this nature, in a time release tablet, can vary as much as 30% of a 75 mg dosage, as shown in the U.S.P., in fact, the potential danger of a total release of 75mg of PPA at one time is prevalent. The wording of **SLOWLY** and **APPROXIMATELY** do not belong in a clinical study of this kind and are totally misleading. Other studies of PPA for determining euphoric effects at recommended dosages.

    1. "Subjects became more alert."
    2. "Therapeutic doses of PPA do not produce the euphorigenic or stimulant subjective effects **that characterize drugs of abuse**." (one of the drugs used as a **comparative** was **L.S.D.**). Yet, the conclusion of the study that was sent to the FDA, with a Citizen's Petition by the sponsoring drug company stated "**no euphoric effects or stimulatory effects were manifested in subjects treated with PPA compared to a placebo**". The above quote is not only misleading, it is totally false.

The FDA Office of Over-The-Counter Drug Evaluation and the NDMA has been aware of this for sometime (letters from Caprice Greystoke have been sent to the NDMA and the FDA, advising them of the above, since August of 1993, please refer to **Caprice Greystoke's Citizen's Petition of August 1, 1994**, Dockets Numbered 81N-022 and 76N-052N - also **September 20, 1994, Amendment to Citizen's Petition** Dockets Numbered 81N-022/CP17 and 76N-052N/CP15).

Referring to items 1, 2, 3 and 4 of this letter enclosed please find the following **pages** from:

Above Mentioned Citizen's Petition
Page 5, Sections B.7. (Reference A.5.) and B.8. (Reference A.6. and A.6.a.)
Dr. Rhodes report, (Reference A.4. pages 1,3,4,5)

Above mentioned Amendment to Citizen's Petition
Page 6, Numbers 10 and 11
Page 8, Conclusion of Statement of Grounds

The above statements and enclosures represent obvious conflicts of interest. For this Proposed Rule to become effective six months after publishing of Final Rule is ludicrous. This by all means should be made retroactive, so that changes or inaction to correct monographs and protocols, that were due to conflicts of interest such as Weintraub, Gilbertson apparent collusion with the NDMA, should be investigated thoroughly and if they have participated in these deceptions they should be forced to resign. The drug companies and the lobby that represent them, if they are party to these deceptions, should be prosecuted.

When a conflict of interest involving an agency that regulates medication betrays a public trust and endangers lives, the strictest of measures should be taken. That means today, tomorrow and yesterday.

Sincerely,

John Spector, CEO

cc: Vice President Al Gore
First Lady Hillary Rodham Clinton
Office of the Inspector General.
Dr. David Kessler
Ms. Mary Martin
Senator Diane Feinstein
Senator Orin Hatch
Congressman Henry Waxman
Congressman Michael Huffington
Congressman Ron Packard
Congressman Ron Wyden
Dr. Christopher T. Rhodes
Mr. Gordon Bowley
Mr. David Weeda
Mr. David Durkin
ABC John Stossel, 20/20
CBS Dan Rather, 48 Hours
NBC Katherine Couric, "NOW"
ABC Sam Donaldson, Prime Time
CBS Mike Wallace, 60 Minutes
NBC Stone Phillips and Jane Pauley, Dateline
NBC Maria Schriver, First Person

B.7. Reference A.5. The Weintraub study was available to the FDA in 1986 to support its proposed ban of extended release and approval of immediate release PPA (August 8, 1991) and was conducted by Dr. Michael Weintraub then employed in 1986 to head this study, by Ciba Geigy makers of Acutrim an extended release weight control product. Early in 1993, (his appointment was known months in advance), Dr. Michael Weintraub was made Director of OTC Drug Evaluation (Gilbertson's superior), and the FDA reversed itself 180° to as to approve extended release, but disapprove immediate release. The appointment of Dr. Weintraub and the immediate reversal of the FDA position, demonstrates a glaring conflict of interest without regard to consumer safety.

B.8. Reference A.6. and A.6.a. Just as asserted above that the NDMA dictates FDA policy so too does the NDMA dictate FDA labeling policy and protocol as shown by the NDMA letter dated January 14, 1993 to Gilbertson, and Gilbertson's letter to the NDMA dated March 9, 1993. Gilbertson's letter of January 14, 1993 makes reference to a meeting between the FDA and the NDMA on November 9, 1992, that makes it apparent that the reversal of extended release and immediate release policy had been decided by that date of the November 9, 1992 meeting. The NDMA in the past had assured the agency that 50mg was a safe dosage to be taken at one time and 150mg to 200mg was safe in any twenty-four hour period. The FDA is relying on an unreliable source. The NDMA still maintains that a single dose of 25mg to 37mg is safe. On the contrary, both the NDMA and the FDA had reliable information that those dosages are mood changing and unsafe (See reference A.8. and A.9.). **Since 86% of the users of PPA weight control products are women, this is one more case of disregarding their safety in favor of profits.**

The FDA is now in the process or has already approved the NDMA protocol to test the possible connection between PPA and strokes. It appears that the fox is watching the hen house!

O.T.C. Phenylpropanolamine Weight Control Products

1. Acting at the request of Mr. John Spector of Caprice Greystoke, I have carefully examined data pertinent to O.T.C. Phenylpropanolamine weight control products and the relationship of a Caprice Greystoke product containing a solution of Phenylpropanolamine at a concentration of 5 mg per metered spray to other O.T.C. products for weight control containing Phenylpropanolamine.

2. I have thirty years experience in the design and evaluation of drug delivery systems. I have published approximately two-hundred research papers on drug topics and I am the editor of three books on drugs, one of which *Modern Pharmaceutics*, now in preparation for its third edition, has attained an international reputation as a standard text on drug products. I am presently in my third quinquenium of service as a member of the *United States Pharmacopoeia* (USP) Committee of Revision: I am a member of two USP Sub-committees, viz (1) Bioavailability, Bioequivalence and Dissolution and (2) Excipients. (USP is the compendium recognized by the U.S. Congress and some twenty-seven foreign countries as providing official standards for drug substances, drug products and devices). Also, I am designated as a Special Government Employee for my work on the FDA Expert Advisory Committee on Generic Drugs. I am a Fellow of the American Academy of Pharmaceutical Sciences.

toxic symptoms can result from "dose dumping". In order to try to reduce or eliminate dose dumping USP imposes dissolution specifications for extended release products which are more extensive than those imposed on class a immediate-release products.

4. FDA has published data[1] concerning the use of Phenylpropanolamine as an O.T.C. product for weight control. At the time of writing (June 1994) FDA policy is that existing data are inadequate to support the use of immediate-release products but that the data are sufficient to justify the use of a controlled-release product. This policy represents a dramatic turn-around from previous agency policy which was that immediate-release products were safe and effective but that timed-release products were not approvable. It was only after a process of intense lobbying by pharmaceutical companies, some of which have very large sales of controlled-release Phenylpropanolamine products, that agency policy showed a 180° change of course. There has been extensive comment on the agency successive iterations of policy on this matter[2].

   The current FDA policy for the use of Phenylpropanolamine in O.T.C. weight control is that the drug is effective at a daily dose of 75 mg in a controlled-release dosage form.

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[1] See letter by William E. Gilbertson of the FDA office of O.T.C. Drug evaluation dated 20 May 1994 addressed to Dr. R. William Sotter of NPDA and references quoted therein.

[2]See for example, *Federal Register* volume 56, number 153, Thursday 8 August 1991 pages 37794-37795 (Exhibit One)

5. The 20 May 1994 letter written by Dr. Gilbertson referred to five publications which report the results of studies of the use of Phenylpropanolamine for weight control. Whilst in full agreement with the general conclusion that their studies clearly support the contention that the drug Phenylpropanolamine is effective when used at a daily dose of 75 mg for O.T.C. weight control, the extent to which their papers can be reasonably used in support of the conclusion that controlled-release Phenylpropanolamine products are effective but that immediate-release products may not be effective is highly questionable. The five studies[3-7] do indeed provide powerful support to the contention that 75 mg of

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[3] Bradley, M.H., "Double Blind Safety and Efficacy Evaluation of Phenylpropanolamine HCL in Obese Patients with controlled Hypertensive Disease," unpublished study in Comment No. RPT7, Docket No. 81N-0022, Dockets Management Branch.

[4] Weintraub, M. etal. "Phenylpropanolamine OROS (Acutrim) vs. Placebo in Combination with Caloric Restriction and Physician-Managed Behavior Modification," Clinical Pharmacology and Therapeutics, 39:501-509, 1986, in Comment No. RPT7, Docket No. 81N-0022, Dockets Management Branch.

[5] Schteingart, D., "A Double-Blind Clinical Evaluation of the Anorectic Activity of Phenylpropanolamine (75 mg) Compared with Placebo in the Treatment of Exogenous Obesity," unpublished study in Comment No. CP11, Docket No. S1N-0022, Dockets Management Branch.

[6] Greenway, F, "A Double-Blind Clinical Evaluation of Phenylpropanolamine (75 mg) compared with Placebo in the Treatment of Exogenous Obesity," unpublished study in Comment No. CP11, Docket o. 81N-0022, Dockets Management Branch.

[7] Atkinson, R., "A Double-Blind Clinical Evaluation of the Anorectic Activity of Phenylpropanolamine (75 mg) Compared with Placebo in the Treatment of Exogenous Obesity," unpublished study in comment No. CP14, Docket No. 81N-0022, Dockets management Branch.

Phenylpropanolamine is indeed effective in the OTC for weight control. However, none of the five papers provides comprehensive, reliable data on either the *in vitro* release profiles of the products nor the drug plasma concentration time profiles. Thus, we have no direct information on how specific the control of release is in these products, nor do we have any assurance that the release profiles of different controlled-release Phenylpropanolamine products are essentially the same or statistically significantly different. Probably the best paper of the five, that by Weintraub and his co-workers does specify that the Acutrim (Ciba-Geigy) product used in their study has a loading dose (immediate release) of 20 mg while "the remaining 55 mg leave the OROS tablet slowly over approximately 16 hours."

In his 20 May 1994 Dr. Gilbertson points out that the Bradley study "cannot be fully analyzed and interpreted, the results cannot be considered conclusive". Thus, the case for the approval of the extended-release versions of Phenylpropanolamine rests primarily on the studies reported by Weintraub, Schteingart, Greenway and Atkinson. It is interesting to note that the Weintraub paper was published in 1986; the Schteingart study was completed in December 1986; the Greenway report was issued in December 1989 and the Atkinson report issued in September 1991. Thus, it would not be easy to argue that the Agency's abrupt change of policy was caused by the recent availability of a plethora of new top quality, evidence which overwhelmingly proved the safety and efficacy of extended release Phenylpropanolamine products for weight control to the exclusion of

10.) On August 8, 1991, Federal Register Volume 56, Number 153, Page 37795, the miscellaneous internal panel recommended the proposed banning of time release capsules, for weight control, containing PPA and the approval of immediate release. **The management** (drug manufacturers) **argued** that the **cost** of a New Drug Application (N.D.A.) for time release would be between 50 million and 150 million. The FDA rejected management's arguments; however, on May 20, 1994, Gilbertson's letter completely reversed the FDA's position without the benefit of an expert advisory committee, **or any new studies,** and acquiesced to drug companies by placing PPA in Category III, that allowed the drug companies, merely to apply for a perfunctory N.D.A. for time release, without having to prove safety and with effectiveness being accepted. The obvious perception is, that this branch of the FDA is more interested in the profits of the drug companies than the safety of the public.

11.) Final Rule, Volume 59, Number 162, Page 43386, August 23, 1994, Final Monograph for Nasal Decongestant is made and PPA is deferred back to 1985 and from 1985 back to 1976, allowing 150 mg of PPA over a 24 hour period in immediate release and time release. There is absolutely no logic in disallowing immediate release of 25 mg PPA in a four hour period for weight control but allowing the exact same dosage of PPA for nasal decongestants. Similarly, there is no logic in the FDA position that dosages of 75 mg of PPA per twenty-four hour period are considered not safe for immediate release weight control but that 150 mg of PPA, for a twenty-four hour period, in immediate release nasal decongestant is safe. (See page 3, paragraph 3.)

Therefore it is necessary to reduce the dosage of PPA, in both these categories, to 12.5 mg administered more frequently, every two hours, and the mandatory banning of time release to ensure consumer safety and the prevention of dose dumping.

CONCLUSION OF STATEMENT OF GROUNDS

To be added to Citizen's Petition Conclusion of Statement of Grounds

Caprice Greystoke is in total disagreement that the Non-prescription Drug Manufacturers Association (NDMA), which has a vested interest, should be a party to any of the testing for the safety of PPA. The NDMA has been less than forthright in its evaluation of dosages in the past and there is no reason to believe that it will be any more forthright in the future. The safety study of PPA should be made by a panel of independent experts selected by the Office of the Inspector General (OIG) and paid for by all the drug companies that use PPA. If this study indicates that there is an adverse connection between recommended dosages of immediate release products containing PPA or the overdosing by dose-dumping from extended release products containing PPA, then the monograph should be changed to reflect the results of these studies. Moreover, since the FDA and the NDMA have been unwilling to reduce the dosages of PPA to a proven safe level, these results should be published broadly so appropriate legal action can be taken, against those two organizations and its officals, by those individuals and their families who have suffered from the FDA's conflict of interest decisions.

FOLLOW THROUGH OF CITIZEN'S PETITION
CONCLUSION OF STATEMENT OF GROUNDS

Cover letter and Citizen's Petition sent in addition to previous 15 cc's:

16.) Office of the Inspector General.

17.) ABC John Stossel, 20/20.

18.) CBS Dan Rather, 48 Hours.

19.) NBC Katherine Couric, "NOW".

20.) ABC Sam Donaldson, Prime Time.

21.) CBS Mike Wallace, 60 Minutes.

22.) NBC Stone Phillips and Jane Pauley, Dateline.

23.) NBC Maria Schriver, First Person.

Cover letters and Citizen's Petition were sent to all above, as stated in Citizen's Petition CONCLUSION OF STATEMENT OF GROUNDS: Inasmuch as the FDA has not chosen to answer it, so that Caprice Greystoke could include its response, this amendment is being sent to all of the prevoius cc's and the cc's listed in this amendment.